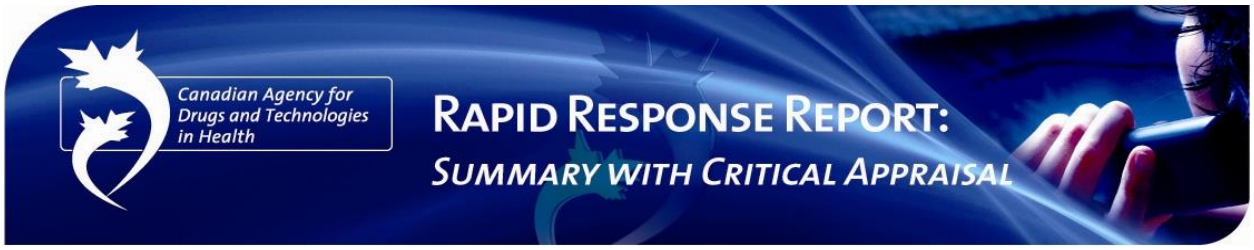


TITLE: Pharmacologic Management of Patients with ADHD: A Review of Guidelines

DATE: 18 March 2016

CONTEXT AND POLICY ISSUES

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder that affects 5% to 12 % of children and approximately 60% to 65% of children with ADHD continue to exhibit the syndrome into adulthood.[1,2] According to the Canadian ADHD Resource Alliance (CADDRA), the prevalence of ADHD in adults is estimated to be 4.4%, with less than 12% of patients able to obtain services even at the primary care level.[3]

ADHD medication improves symptoms of ADHD and ameliorates associated conduct problems in children and adults. Psychostimulants, which relieve symptoms by increasing intra-synaptic dopamine, norepinephrine and serotonin, are the mainstay of ADHD treatment.[4-7] Stimulant drugs approved for use to manage ADHD in Canada are amphetamine-based psychostimulants (Dexedrine, Adderall, and Vyvanse) and methylphenidate-based psychostimulants (methylphenidate, Biphentin and Concerta). Strattera (atomoxetine) and Intuniv (guanfacine XR) are two non-stimulant ADHD medications currently approved for use in Canada. Other agents that have been used off-label for ADHD treatment include tricyclic antidepressants, bupropion, selective serotonin reuptake inhibitors, buspirone, and atypical antipsychotic drugs.[3,8]

The aim of this review is to summarize recommendations for the pharmacotherapy of ADHD in children, adolescents, and adults from current evidence-based clinical guidelines to support treatment decisions.

RESEARCH QUESTION

What are the evidence-based guidelines for the pharmacologic management of ADHD in children, adolescents, and adults?

KEY FINDINGS

Stimulant drugs are the first-choice pharmacological treatment for ADHD in children, adolescents, and adults. Atomoxetine is the preferred initial choice of treatment when there is a

risk that stimulant drugs may be abused/misused or diverted. Atomoxetine is also the recommended drug of choice when stimulant ADHD drugs are contra-indicated, ineffective, or poorly tolerated. There is limited evidence to support the efficacy or safety of combination therapy for ADHD comprising stimulant and non-stimulant drugs in patients with inadequate clinical response to monotherapy.

METHODS

Literature Search Methods

A limited literature search was conducted on key resources including Medline, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2011 and February 18, 2016.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Children, adolescents, or adults with ADHD
Intervention	Guidelines for pharmacologic management
Comparator	None
Outcomes	Recommendations for the pharmacotherapy of ADHD
Study Designs	Evidence-based Clinical Guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to January, 2011. The Third edition of the Canadian ADHD Practice (CAP) guidelines,[3] produced by the Canadian ADHD Resource Alliance (CADDRA) was not included since it, has previously been reviewed by CADTH[9] and does not warrant a full assessment in this report.

Critical Appraisal of Individual Studies

The guidelines were assessed with the AGREE II instrument,[10] and the strengths and limitations of each included guideline were described narratively.

SUMMARY OF EVIDENCE

Quantity of Research Available

A total of 52 citations were identified in the literature search. Following screening of titles and abstracts, 42 citations were excluded and 10 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search. Of these 13 potentially relevant articles, 10 publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

A brief summary of the previous CADTH report[9] on the 2011 version of the CAP guideline, together with a summary table indicating the place in therapy of various ADHD drugs is presented in Appendix 5.

Summary of Study Characteristics

Study Design

One guideline by the British Association for Psychopharmacology[4] was developed by a committee of experts in a wide range of aspects of ADHD in children, adolescents and adults. Evidence for the recommendations were collected from relevant published and unpublished literature with emphasis on meta-analysis, systematic reviews, and randomized controlled trials.[4] Evidence was appraised according to defined criteria and the recommendations of the guidelines were made by consensus during a one-day conference of the experts. Observers from pharmaceutical companies provided clarification on unpublished data from clinical trials, post-marketing surveillance of drug use, and marketing authorization for specific drugs, but they were not participants in the proceedings or in the drafting of the guidelines.[4]

Another guideline by the American Academy of Pediatrics (AAP)[5] was developed by a subcommittee comprising primary care pediatricians and developmental-behavioral pediatricians. The AAP collaborated with several organizations to form this guideline development subcommittee, which included representatives from the American Academy of Child and Adolescent Psychiatry, the Child Neurology Society, the Society for Pediatric Psychology, the National Association of School Psychologists, the Society for Developmental and Behavioral Pediatrics, the American Academy of Family Physicians, and Children and Adults with Attention-Deficit/Hyperactivity Disorder (CHADD), as well as an epidemiologist from the Centers for Disease Control and Prevention (CDC).[5] The group systematically reviewed literature for changes that had occurred in practice and issues that had been identified since the previous AAP guidelines were published in 2001. Recent reviews from AHQR (2011) and CDC were the main basis for the treatment-related evidence, and recommendations for pharmacological intervention were based on available new information regarding the long-term efficacy and safety of medications approved by the United States Food and Drug Administration for the treatment of ADHD.[5]

One guideline by the Academy of Medicine, Singapore and Ministry of Health, Singapore (AMS–MOH)[7] was developed by a multi-disciplinary workgroup of psychiatrists, pediatricians, educational psychologists, a medical social worker, a pharmacist, an advanced practice nurse and parent representative. Details about the source of evidence and how evidence was collected and synthesized were not provided.[7]

In each guideline, the quality of evidence was graded and categorized using clearly defined criteria; and the strength of recommendations was based on supporting evidence. Further details of the grading and characterization of recommendations and the quality of evidence supporting them are provided in Table A1 of Appendix 2.

Country of Origin

The British Association for Psychopharmacology guideline[4] was developed in the United Kingdom and published in 2014, while the AAP guideline[5] was developed in the United States of America and published in 2011. The AMS–MOH guideline[7] was developed in Singapore and published in 2014.[7]

Intended users/Target population

All guidelines[4,5,7] were intended for use by clinicians who deliver clinical care to patients with ADHD. In addition, one guideline[4] was also intended for use by those who commission treatment or are otherwise involved in the diagnosis and treatment of ADHD. All three guidelines,[4,5,7] were meant to apply to children and adolescents (≤18 years) with ADHD. In addition, one guideline[4] was also meant to apply to adults with ADHD. While two of the guidelines[5,7] specified the inclusion of preschool children (4 to 5 years of age) and older children, the other guideline[4] did not make such distinction between children.

Interventions and Comparators

All guidelines[4,5,7] aimed to provide evidence-based information for the diagnosis and treatment of ADHD. They discussed both pharmacologic and non-pharmacologic interventions options such as cognitive training and behavioral intervention approaches aimed to improve neuropsychological deficits involving working memory or executive functioning. To answer the specific question of this review, discussions have been limited to pharmacological interventions, classified broadly into stimulant and non-stimulant drugs.

Outcomes

Outcomes of interest were evidence-based recommendations for the pharmacological treatment of ADHD in clinical practice. The recommendations in all of the guidelines[4,5,7] were graded based on the supporting evidence.

Summary of Critical Appraisal

All guidelines[4,5,7] clearly described their scope and purpose, stating the overall objectives, the professionals for whom the guidelines were developed for and the target populations to whom they were meant to apply to. Each guideline[4,5,7] was developed by a group of individuals with relevant expertize in a wide range of aspects of ADHD, thus, well representing the target users of the guidelines. Two guidelines[4,7] also had input from target populations to whom the guidelines were meant to apply to. However, one guideline[5] had no indication that the views and preferences of the target population had been sought or incorporated.

Two guidelines[4,5] collected and synthesized evidence from comprehensive systematic reviews of relevant literature, and recommendations were arrived at through consensus. One guideline[7] did not specify how its recommendations were derived or how the evidence for its

recommendations were gathered and synthesized. In each of the guidelines,[4,5,7] the recommendations were ranked based on the quality of available evidence, which had been appraised using a clearly defined scheme. Two guidelines[5,7] were appraised internally by independent external experts, with comments considered before the final guidelines were published. In addition, one guideline[5] was developed by a collaborative subcommittee of experts with representatives from 10 professional or governmental organizations, which likely broadened the perspective and increased the rigor of development. One guideline[7] received comments and endorsements from professional medical associations. For one of the guidelines,[4] it was unclear whether it was independently appraised by external experts or endorsed by a professional organization.

Each guideline[4,5,7] clearly presented the key recommendations and the options for the management of ADHD were well described. All included guidelines[4,5,7] were developed in foreign countries and meant for clinical practice outside Canada. However, their recommendations were generally similar to the CAP guideline recommendations in the choice of stimulant drugs as first-line, and non-stimulant drugs as second-line pharmacotherapy. A notable difference is that while the guidelines[4,5,7] included in this review considered stimulant drugs in general as first-line therapy for ADHD, the CAP guideline listed extended-release stimulant drugs as first-line, while short-acting and intermediate-acting stimulant drugs were listed as second-line drugs. Each guideline[4,5,7] specified the timeline and/or conditions for an update or revision.

In two guidelines,[4,5] some members of the guideline development group had benefited from pharmaceutical companies by way of consultation fees, honoraria for speaking, study and research grants, as well as travel and conference support. In one guideline,[7] there was no information provided to allow for the assessment of potential competing interest of members of the guideline development workgroup, and it was unknown whether the guideline development was sponsored by a body with the potential to influence its content. In another guideline,[4] pharmaceutical companies sponsored a meeting by the experts who developed the guideline to reach consensus. However the authors stated that the participants did not receive fees or honoraria for participation and the guideline represented their independent views.

Summary of Findings

What are the evidence-based guidelines for the pharmacologic management of ADHD in children, adolescents, and adults?

One guideline[5] reported that the evidence supporting the effectiveness of ADHD drugs is strongest for stimulant medications followed by atomoxetine, extended-release guanfacine, and extended-release clonidine – in that order.

All guidelines[4,5,7] recommended that in children (including preschool children) with ADHD, psychosocial/behavioral therapy should be the initial intervention; and pharmacological treatment should be considered for those with moderate symptoms of ADHD who have not responded to psychological/behavioral interventions. However, one guideline[4] strongly recommended that all children with severe ADHD should be offered pharmacological treatment. All guidelines[4,5,7] were in agreement with a strong recommendation for stimulant medication as the treatment of choice for children and adolescents when pharmacological intervention was needed. Only one of the guidelines[4] included adults as a target population, and it recommended stimulants as first-line treatment for adults with ADHD.

There was a strong recommendation in all guidelines[4,5,7] to consider atomoxetine for the treatment of ADHD symptoms when there is increased risk of abuse/misuse or diversion with stimulant medication use. Two guidelines,[4,7] stated that the risks of abuse can be largely avoided by use of long-acting formulations. Therefore, they recommended (with weak evidentiary support) to consider extended-release stimulant drugs instead of immediate-release formulations if there is concern about medication abuse. One guideline[7] recommended atomoxetine as initial choice of treatment if stimulant treatment is contra-indicated, ineffective or poorly tolerated; or in the presence of anxiety disorders or severe tics.

Dose titration of ADHD medication to achieve maximum benefit with minimum adverse effects was recommended by all guidelines.[4,5,7] One guideline[7] recommended regular assessment of response and side effects to decide if medication should be continued, with regular monitoring of height, weight and body mass index (BMI) of children receiving treatment with methylphenidate (stimulant medication) or atomoxetine. Two guidelines[4,7] recommended that drug holidays (a medication-free period during its systematic use) can help limit adverse effects, with one guideline[5] adding that drug holidays may be useful to ascertain the need to continue treatment. Common adverse effects of ADHD medication include social withdrawal, irritability and crying, and reduced growth rates.[7] Adverse effects reported with stimulant ADHD drugs include appetite loss, abdominal pain, headaches, and sleep disturbance, while adverse effects associated with atomoxetine include initial somnolence and gastrointestinal tract symptoms, decrease in appetite, increase in suicidal thoughts, and hepatitis.[5]

All guidelines[4,5,7] stated that evidence was not sufficient to support the efficacy or safety of co-administrations of stimulants and non-stimulant drugs as therapy for ADHD in patients who have not responded adequately to monotherapy. One guideline[7] recommended against the combined use of methylphenidate (a stimulant drug) and atomoxetine for the treatment of ADHD symptoms. However, one guideline[4] stated that there is some evidence (level Ib, defined as evidence from at least one RCT) to support beneficial effects of combinations of psychostimulants and guanfacine in children resistant to stimulants alone. It must be noted that in Canada, Intuniv XR (guanfacine hydrochloride extended-release) has been approved for use as an adjunctive therapy to psychostimulants for the treatment of ADHD children and adolescents, aged 6 to 17 years, with a sub-optimal response to psychostimulant. However, Intuniv XR has not been systematically studied in and is therefore not indicated for use in adults (over 18 years of age).[11]

Limitations

All of the included guidelines[4,5,7] were developed in foreign countries and meant for clinical practice outside Canada. However, the recommendations in these guidelines are similar to the recommendations of the CAP guideline produced by CADDRA. A notable difference is that while the guidelines[4,5,7] included in this review considered stimulant drugs in general as first-line therapy for ADHD, the CAP guideline listed extended-release stimulant drugs as first-line, while short-acting and intermediate-acting stimulant drugs were listed as second-line drugs. This separation seems to have been made to promote adherence and was not based on any evidence of one formulation of stimulant drug being more effective than the other. Atomoxetine is considered a second-line drug in the CAP guideline and in the guidelines included in this review. Thus, it is unlikely that the country of origin of the guidelines included in this review would present significant generalizability challenges to users in Canada.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING

There is agreement among the included guidelines[4,5,7] that stimulant ADHD drugs be considered as first-choice pharmacological treatment both in children and adults. One guideline[5] reported that the evidence supporting the effectiveness of ADHD drugs is strongest for stimulant medications followed by atomoxetine, extended-release guanfacine, and extended-release clonidine; in that order. The included guidelines[4,5,7] also agree that atomoxetine should be preferred as initial choice of treatment when there is concern about risk of abuse/misuse or diversion stimulant drugs. Other conditions under which atomoxetine would be the drug of choice include contraindications, ineffectiveness, poor tolerance of stimulants; or, in the presence of anxiety disorders or severe tics. While co-administration of stimulant and other drugs have been used off-label as an option for patients lacking or showing limited clinical response, there is insufficient evidence to support the efficacy or safety of such combination therapy.

PREPARED BY:
Canadian Agency for Drugs and Technologies in Health
Tel: 1-866-898-8439
www.cadth.ca

REFERENCES

1. Lopez FA, Leroux JR. Long-acting stimulants for treatment of attention-deficit/hyperactivity disorder: a focus on extended-release formulations and the prodrug lisdexamfetamine dimesylate to address continuing clinical challenges. Atten Defic Hyperact Disord [Internet]. 2013 Sep [cited 2016 Mar 11];5(3):249-65. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3751218

2. McDonagh MS, Peterson K, Thakurta S, Low A. Drug class review: pharmacologic treatments for attention deficit hyperactivity disorder: final update 4 report [Internet]. Portland (OR): Oregon Health & Science University; 2011 Dec. [cited 2016 Mar 11]. Available from: http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0034136/pdf/PubMedHealth_PMH0034136.pdf

3. Canadian ADHD practice guidelines (CAP-guidelines) [Internet]. 3rd ed. Toronto: Canadian Attention Deficit Hyperactivitiy Disorder Resource Alliance (CADDRA); 2011. [cited 2016 Mar 11]. Available from: http://www.caddra.ca/pdfs/caddraGuidelines2011.pdf

4. Bolea-Alamanac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2014 Mar;28(3):179-203.

5. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, et al. ADHD: clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics [Internet]. 2011 Nov [cited 2016 Feb 22];128(5):1007-22. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4500647/pdf/nihms701937.pdf

6. Attention deficit hyperactivity disorder: diagnosis and management [Internet]. London: National Institute for Health and Care Excellence; 2008. [cited 2016 Feb 22]. (NICE guidelines [CG72]). Available from: http://www.nice.org.uk/guidance/cg72/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-975625063621

7. Attention deficit hyperactivity disorder [Internet]. Singapore: Ministry of Health, Singapore; 2014 May. [cited 2016 Feb 26]. Available from: https://www.moh.gov.sg/content/dam/moh_web/HPP/Doctors/cpg_medical/current/2014/adhd/ADHD%20CPG_Booklet.pdf

8. Gibson AP, Bettinger TL, Patel NC, Crismon ML. Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. Ann Pharmacother. 2006 Jun;40(6):1134-42.

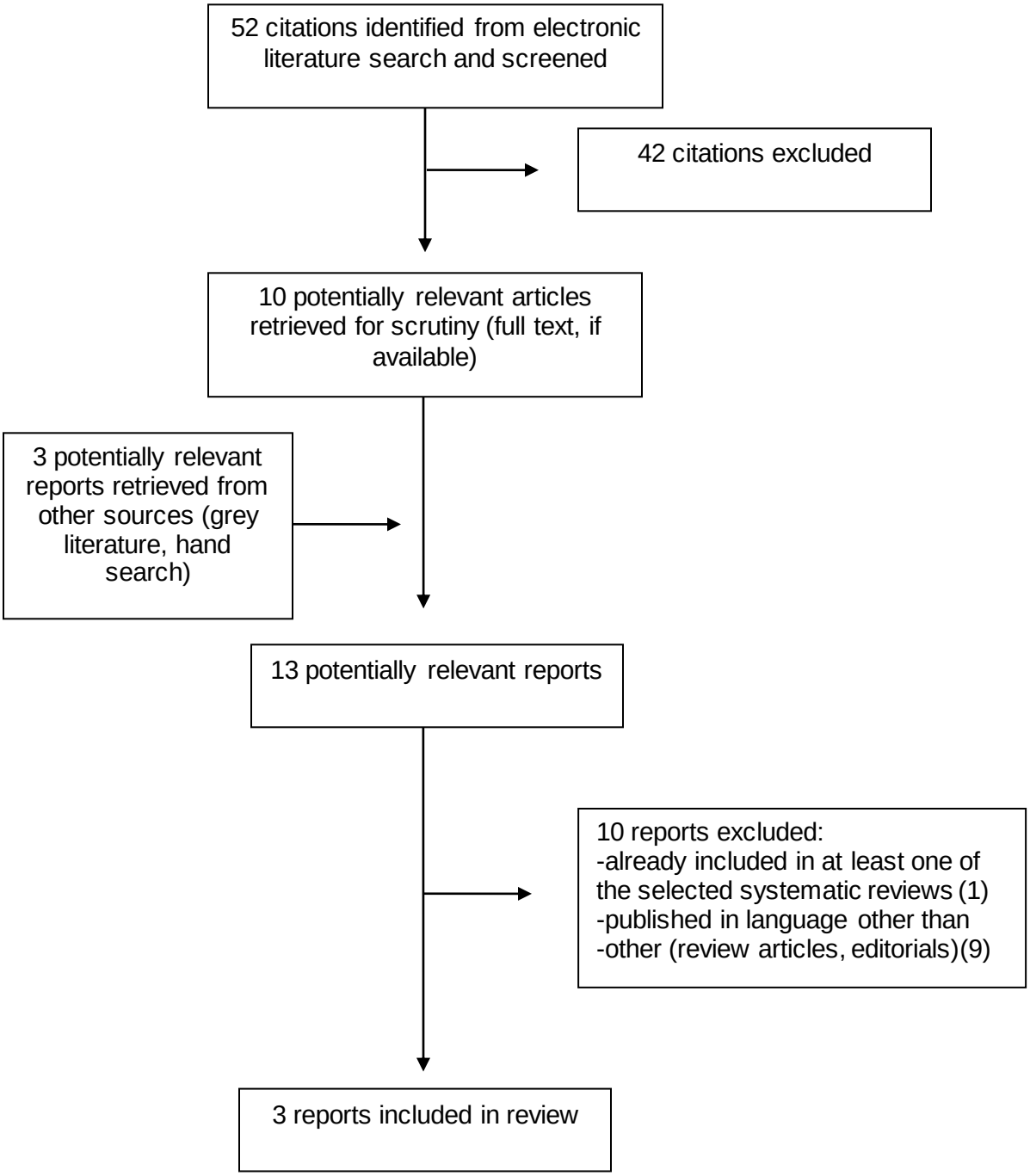
9. Quality assessment of the Canadian Attention Deficit Hyperactivity Disorder Resource Alliance ADHD practice guidelines for children, adolescents and adults with ADHD [Internet]. Ottawa: CADTH; 2011 May 2. [cited 2016 Mar 17]. (Rapid response report:

summary with critical appraisal). Available from: https://www.cadth.ca/sites/default/files/pdf/htis/may-2011/RC0261-000_-_CADDRA_Guidelines_on_ADHD_Final.pdf

10. Brouwers M, Kho ME, Browman GP, Burgers JS, Cluzeau F, Feder G, et al. AGREE II: advancing guideline development, reporting and evaluation in healthcare. CMAJ [Internet]. 2010 Dec [cited 2016 Mar 11];182(18):E839-E842. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3001530/pdf/182e839.pdf

11. PrIntuniv XR®* (guanfacine hydrochloride extended-release tablets): 1 mg, 2 mg, 3 mg, 4 mg guanfacine (as guanfacine HCl) [product monograph]. Saint-Laurent (QC): Shire Pharma Canada ULC; 2016 Feb 25.

APPENDIX 1: Selection of Included Studies



APPENDIX 2: Characteristics of Included Publications

Table A1: Characteristics of Included Guidelines [a]

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
Academy of Medicine, Singapore and Ministry of Health, Singapore (AMS–MOH), 2014[r]						
Professional practitioners/children and adolescents ADHD patients in Singapore	A framework to diagnose and plan treatment, and to inform practitioners about the level of evidence available to aid decisions about medication use.	Evidence-based recommendations for the pharmacological treatment of ADHD in clinical practice	A multi-disciplinary workgroup of psychiatrists, pediatricians, educational psychologists, a medical social worker, a pharmacist, an advanced practice nurse and a parent representative were involved in the development of the CPG. No details were provided about sources of evidence and methods of evidence collection and synthesis.	Quality of evidence was ranked as follows: **1^{++}**: High quality MAs, SRs of RCTs, or, or RCTs with a very low risk of bias **1^{+}**: Well conducted MAs, SRs of RCTs, or RCTs with a low risk of bias **1^{-}:** MAs, SRs of RCTs, or RCTs with a high risk of bias **2^{++}:** High quality SRs of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the	The strength of recommendations was categorized as: **A:** At least one MA, SR of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or a body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results **B:** A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 1^{++} or 1^{+} **C:** A body of evidence including studies rated as 2^{+}, directly applicable to the	The following organizations commented on and endorsed the guidelines: - Academy of Medicine, Singapore - Chapter of Psychiatrists, Academy of Medicine, Singapore - College of Paediatrics and Child Health, Singapore, and - College of Family Physicians Singapore

Table A1: Characteristics of Included Guidelines [a]

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
				relationship is causal **2^{+}:** Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal **2-:** Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal **3:** Non-analytic studies, e.g. case reports, case series **4:** Expert opinion	target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as 2^{++} **D:** Evidence level 3 or 4; or extrapolated evidence from studies rated as 2^{+} GPP: Recommended best practice based on the clinical experience of the guideline development group.	
Bolea-Alamanac, 2014 – British Association for Psychopharmacology[4]						
Clinicians and user representatives who deliver clinical care, commission treatment or are otherwise	Guidelines for the treatment of ADHD in general practice, pediatric practice and psychiatric and	Recommendations for improved pharmacological treatment of ADHD in children and	A committee of experts in a wide range of aspects of ADHD in children, adolescents and	Quality of evidence was categorized as follows:	Strength of recommendation was categorized as follows:	A draft guideline and transcript of discussion session were circulated for

Table A1: Characteristics of Included Guidelines [a]

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
involved in the diagnosis and treatment/Children, adolescents and adults with ADHD	psychopharmacologic practices.	adults following translation of recent research to generate expert consensus recommendations in the field of ADHD	adults collected evidence from relevant published and unpublished literature with emphasis on MAs, SRs and RCTs. Observers provided clarification on unpublished data from clinical trials, post-marketing surveillance of drug use, and marketing authorization. Evidence selection was based on consensus.	**Ia:** Evidence from meta-analysis of RCT **Ib:** Evidence from at least one RCT **IIa:** Evidence from at least one controlled study without randomization **IIb:** Evidence from at least one other type of quasi-experimental study **III:** Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies **IV:** Evidence from expert committee reports or opinions and/ or clinical experience of respected	**A:** Directly based on category I evidence **B:** Directly based on category II evidence or extrapolated from category I evidence **C:** Directly based on category III evidence or extrapolated from category II evidence **D:** Directly based on category IV evidence or extrapolated from category III evidence **S:** Standard of clinical care	comments, with the final guideline reflecting the views of participants at a one day conference for to achieve consensus.

Table A1: Characteristics of Included Guidelines [a]

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
				authorities		
Meyer, 2011 – American Academy of Pediatrics [5]						
Clinicians/ Children (including 4 to 5 years old) and adolescents (≤18 years)	Guideline and process-of-care algorithm for the diagnosis, evaluation, and treatment of ADHD in children 4 through 18 years of age	Evidence-based recommendations for the pharmacological treatment of ADHD in clinical practice	A subcommittee comprising primary care pediatricians, developmental-behavioral pediatricians, and representatives from the AACAP, CNS, SPP, NASP, SDBP, AAFP, CHADD; and CDC systematically reviewed literature for changes that have occurred in practice and issues that have been identified since the previous guidelines were published. Recent reviews from AHQR (2011) and CDC were the main basis for the treatment-related evidence and recommendations for pharmacological intervention considered available new information regarding the long-term efficacy and safety of medications approved by the US	The quality of evidence supporting each recommendation and the strength of each recommendation were assessed by the committee member most experienced in epidemiology and graded according to AAP policy. The evidence quality was categorized as follows: **A:** well-designed RCTs or diagnostic studies on relevant population **B**: RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies	Recommendation were described as action statements classified as "strong recommendation" or "recommendation" or "optional" and defined as follows: **Strong recommendation**: were based on high-to-moderate-quality (A to B) scientific evidence and a preponderance of benefit over harm. **Recommendation:** were based on high-to-moderate-quality (B to C) scientific evidence and a preponderance of benefit over harm. **Option-level action statements:** were based on lesser-quality evidence (D) or limited data and expert consensus or high-quality evidence with a balance	The draft guidelines and process-of-care algorithm were peer reviewed internally, and by external organizations and individuals identified by the subcommittee. Reviewer comments were compiled and reviewed by the chairperson, and relevant changes were incorporated into the draft, which was then reviewed by the full committee before the final document.

Table A1: Characteristics of Included Guidelines [a]

Objectives			Methodology			
Intended users/ Target population	**Intervention and Practice Considered**	**Major Outcomes Considered**	**Evidence collection, Selection and Synthesis**	**Evidence Quality and Strength**	**Recommendations development and Evaluation**	**Guideline Validation**
			FDA for the treatment of ADHD.	**C:** Observational studies (case-control and cohort design) **D:** Expert opinion, case reports, reasoning from first principles **X:** Exceptional situations in which validating studies cannot be performed and there is a clear preponderance of benefit or harm	between benefits and harms.	

AACAP = American Academy of Child and Adolescent Psychiatry; AAFP = American Academy of Family Physicians; ADHD = attention deficit hyperactivity disorder; AHQR = Agency for Healthcare Research and Quality; CDC = Centers for Disease Control and Prevention; CHADD = Children and Adults with Attention-Deficit/Hyperactivity Disorder; FDA = Food and Drug Administration; GPP = good practice points; MA = meta-analysis; NASP = National Association of School Psychologists; NICE = National Institute for Health and Care Excellence; RCT = randomized controlled trials; SDBP = Society for Developmental and Behavioral Pediatrics SPP = Society for Pediatric Psychology; SR = systematic review;

[a] To answer the specific question of this review, the focus of this Table is mainly on pharmacological therapy of ADHD.

APPENDIX 3: Critical Appraisal of Included Publications

Table A2: Strengths and Limitations of Guidelines using AGREE II[10]

Strengths	Limitations
Academy of Medicine, Singapore and Ministry of Health, Singapore (AMS-MOH), 2014[7]	
• The objective and scope of the guideline were described, indicating that the guideline was meant to be used as a framework by professional practitioners for assessment and diagnosis, and to plan treatment of ADHD in children and adolescents below the age of 18 years old in Singapore. • The guideline was developed by a multi-disciplinary workgroup comprising psychiatrists, pediatricians, educational psychologists, a medical social worker, a pharmacist, an advanced practice nurse and a parent representative. Thus it appears stakeholder involvement was broad-based with input from target populations and target users. • Recommendations were graded based on the quality of available evidence. The quality of evidence was appraised based on a clearly defined scheme. • Key recommendations in the guideline are clearly presented with ADHD management options clearly stated. Advice on how to use pharmacological interventions in ADHD in children and adolescents has been clearly presented, alone with those for dose titration or adjustments (when needed) and monitoring patients for AEs. • Independent experts, experienced as clinicians or researchers in the area of ADHD, reviewed a draft version of the guideline and provided important comments which were considered by the workgroup prior to the final document. The guideline also received comments and endorsements from relevant professional medical associations. • The time-line and/or conditions for updating the guideline were provided.	• The process for developing the guideline was not adequately described. The sources of evidence and the process evidence selection and synthesis were not provided. Further, the methods for formulating the recommendations (consensus or otherwise) were not discussed. • There was no information provided to allow assessment of potential competing interest of members of the guideline development workgroup, and sponsorship for the guideline development was not declared. Thus the editorial independence of this guideline is uncertain.
Bolea-Alamanac, 2014 – British Association for Psychopharmacology[4]	
• The scope and purpose of the guideline were described, specifying the overall objectives, the health question(s) covered by the	• Although the guideline was developed by the BAP council, it was unclear whether it was reviewed by experts external to

Table A2: Strengths and Limitations of Guidelines using AGREE II[10]	
Strengths	**Limitations**
guideline and the population to whom the guideline is meant to apply. • The guideline was developed by a group of experts including psychiatrists, psychologists, pharmacists, clinical and preclinical researchers, and user representatives with expertise in a wide range of aspects of ADHD in children, adolescents and adults. Thus it appears stakeholder involvement was broad-based with input from target populations and target users. • The process for developing the guideline was rigorous, encompassing a comprehensive assessment of current literature on ADHD, ranging from etiological research and neuroimaging to current trends in the development of treatment and services. Recommendations were reached through consensus, and they were ranked based on the quality of available evidence. The quality of evidence was appraised based on a clearly defined scheme. • A draft guideline was circulated to all participants for comments at a one-day conference convened to arrive at a consensus on the guideline. • The time-line and procedure for updating the guideline were provided. • Key recommendations of the guideline were clearly presented along with options for management of the condition. • The guideline provides advice on how to use pharmacological interventions in ADHD in children, adolescents and adults, and advises on careful titration of doses and monitoring patients for AEs.	the guideline development group prior to its publication. Furthermore, there was no indication of endorsement by any professional bodies. • Some members of the guideline development group had benefited from pharmaceutical companies by way of consultation fees, honoraria for speaking, study and research grants as well as travel and conference support. In addition, the expert meeting to gain consensus for the guidelines was in part sponsored by pharmaceutical companies. However the authors stated that the participants did not receive fees or honoraria for participation and the guideline represented the independent views.
Meyer, 2011 – American Academy of Pediatrics[5]	
• The scope and purpose of the guideline were described, with an overall objective to address challenges presented by ADHD for children/adolescents and their families, as well as to serve as a resource for clinicians seeking to diagnose and treat ADHD in children 4 through 18 years of age. • The guideline was developed by a	• Some member of the guideline development group had benefited from pharmaceutical companies by way of consultation fees, honoraria for speaking, study and research grants as well as travel and conference support. However, considering the extensive collaborations involved in the

Table A2: Strengths and Limitations of Guidelines using AGREE II[10]	
Strengths	**Limitations**
collaborative subcommittee of primary care and subspecialty groups including primary care pediatricians, developmental-behavioral pediatricians, and representatives from the AACAP, the AAP, the CNS, the SPP, the NASP, the SDBP, the AFP, and CHADD, as well as an epidemiologist from the CDC. • The process for developing the guideline was rigorous, and involved a multilevel, systematic approach to identify and review relevant literature, as well as a review of the changes in practice that had taken place, and issues that have been identified since 2001, when the previous AAP guidelines on ADHD were published. • The guidelines underwent extensive internal and external peer reviews, and relevant changes were incorporated into the draft following compilation and review by the chairperson. The resulting document was then reviewed by the full committee. • The guideline has clarity of presentation. Key recommendations and options for ADHD management in different age groups were clearly presented. • The time-line and/or conditions for revision of the guideline were specified.	development, the rigor of the process and the extent of internal and external peer reviews applied, it is unlikely that the editorial independence of this guideline was compromised. • There was no indication that the views and preferences of the target population (patients, families and the general public) had been sought or incorporated in the guideline.

AACAP= American Academy of Child and Adolescent Psychiatry; AAFP= American Academy of Family Physicians; AAP= American Academy of Pediatrics; ADHD = attention deficit hyperactivity disorder; AHQR= Agency for Healthcare Research and Quality; BAP = British Association for Psychopharmacology; CDC = Centers for Disease Control and Prevention; CHADD = Children and Adults with Attention-Deficit/Hyperactivity Disorder; FDA = Food and Drug Administration; NASP = National Association of School Psychologists; NICE = National Institute for Health and Care Excellence; SDBP = Society for Developmental and Behavioral Pediatrics SPP = Society for Pediatric Psychology;

APPENDIX 4: Main Study Findings and Author's Conclusions

Table A3: Summary of Findings of Included Studies

Main Guideline Recommendations (*Quality of evidence/Strength of recommendation*) [a]	Author's Conclusions
Academy of Medicine, Singapore and Ministry of Health, Singapore (AMS–MOH), 2014[7]	
• When medication is considered for the treatment of ADHD, methylphenidate should be considered first. (*Grade A/Level 1*$^{+}$) • The use of methylphenidate or atomoxetine in preschoolers should be considered only if psychosocial interventions have failed. Care should be taken to regularly assess response and monitor for side effects, so as to decide if medication should continue to be administered. (*Grade A, Level 1*$^{++}$) • The height, weight and BMI of children receiving treatment with methylphenidate should be regularly monitored (Grade A/Level 1^{++}). • Methylphenidate may be used to treat ADHD in children with comorbid tic disorder but treatment should be stopped if the tics worsen following treatment. (*Grade A/Level 1*$^{+}$) • Methylphenidate may be considered for the treatment of ADHD in individuals who have also been diagnosed with autistic spectrum disorder. Care should be taken to watch for side effects. (*Grade A/Level 1*$^{+}$) • Atomoxetine may be used for the treatment of ADHD symptoms when there is increased risk with methylphenidate use (e.g. high risk of abuse or diversion) (*Grade A/Level 1*$^{+}$) • During treatment with atomoxetine, there should be periodic monitoring of growth (height and weight) and mental state (suicidal thinking). If there is concern about slowing of growth rate, the need for continued medication use should be reviewed and jointly decided with parents, and there may be a need to evaluate for other medical reasons explaining this. (*Grade A/Level 1*$^{++}$) • To improve treatment adherence, treatment should be individualized for each patient with ADHD, and the parents' and their child's preferences should be considered. (*Grade A/Level 1*$^{+}$)	• The guideline points to the importance of considering factors such as the age of the patient, severity of the ADHD symptoms and resultant impairment, co-morbid conditions and safety issues when prescribing pharmacotherapy for ADHD therapy.

Table A3: Summary of Findings of Included Studies	
Main Guideline Recommendations (*Quality of evidence/Strength of recommendation*) [a]	**Author's Conclusions**
• Drug holidays during treatment with methylphenidate may be considered in order to limit adverse effects. Attention deficit hyperactivity disorder symptoms and impairment during the non-medication days should be monitored (*Grade B, Level 1*$^{+}$) • The combination of methylphenidate and atomoxetine should not be used for the treatment of attention deficit hyperactivity disorder symptoms (*Grade C, Level 2*$^{+}$)	
Bolea-Alamanac, 2014 – British Association for Psychopharmacology[4]	
• *General* • Psychostimulants are first-choice pharmacological treatment both in children and adults with quality of evidence for methylphenidate and dexamfetamines reach rated as level Ia compared with the non-stimulant atomoxetine bupropion, clonidine and guanfacine which are rated as level Ib. • Atomoxetine should be preferred as initial choice of treatment if there are any contra-indications to stimulant treatment, when treatment with methylphenidate has been ineffective, or not tolerated, in the presence of anxiety disorders or severe tics, or when there is a risk of misuse or diversion. *(Evidence level IV)* • Co-administration of psychostimulant and other drugs (mainly atomoxetine) is an option for patients showing a limited or lack of clinical response. There is, however, limited evidence supporting either the efficacy or safety of combination therapy. (*Evidence level IV*). *Children and adolescents* • All children with severe ADHD should be offered pharmacological treatment. In addition, consider pharmacological treatment for children with moderate symptoms of ADHD who have not responded to psychological interventions. (*Strength of recommendation A*) • The treatment of choice for children with severe ADHD or moderate ADHD non-responsive to psychological treatments is	• "The present guidelines summarize current literature, generating expert consensus recommendations for the treatment of ADHD in children and adults."[4] page 198 • "ADHD is a common condition with a high societal burden which may be reduced as we gain a better understanding of the disorder through well-targeted research programmes. Research is needed into its aetiology (e.g. the role of gene–environment interactions, nutrition, and the importance of genetic variants), its pathophysiology (e.g. validity of the dopamine hypothesis and connectivity) and its treatment (e.g. use of stimulants in substance use disorder and autism, novel compounds and new psychological treatments)."[4] page 198

Table A3: Summary of Findings of Included Studies	
Main Guideline Recommendations (*Quality of evidence/Strength of recommendation*) [a]	**Author's Conclusions**
psychostimulant medication (*Strength of recommendation A*) • Atomoxetine can be used instead when there is a risk of misuse of psychostimulants by children or the adults supporting the child (*Strength of recommendation S*) • Combinations of psychostimulants and guanfacine have shown benefit in children resistant to stimulants alone (*Evidence level Ib*) • Drug holidays may be useful to ascertain the need of continuation of treatment (*Strength of recommendation S*) *Adults* • Stimulants are first-line treatment for adults with ADHD (*Strength of recommendation A*) • Atomoxetine is considered first-line treatment in patients with substance use disorders (*Strength of recommendation S*) • Careful titration and monitoring of side effects is required, particularly when using stimulants. (*Strength of recommendation A*)	
Meyer, 2011 – American Academy of Pediatrics[5]	
• The primary care clinician should initiate an evaluation for ADHD for any child 4 through 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity (*B/strong recommendation*). • The primary care clinician should recognize ADHD as a chronic condition and, therefore, consider children and adolescents with ADHD as children and youth with special health care needs. Management of children and youth with special health care needs should follow the principles of the chronic care model and the medical home (*B/strong recommendation*). • For pre-school aged children (4 to 5 years of age), methylphenidate may be prescribed if behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. In areas in which evidence-based behavioral treatments are	• "Evidence continues to be fairly clear with regard to the legitimacy of the diagnosis of ADHD and the appropriate diagnostic criteria and procedures required to establish a diagnosis, identify co-occurring conditions, and treat effectively with both behavioral and pharmacologic interventions. However, the steps required to sustain appropriate treatments and achieve successful long-term outcomes still remain a challenge. To provide more detailed information about how the recommendations of this guideline can be accomplished, a more detailed but less strongly evidence-based algorithm is provided as a companion article."[4] page 20

Table A3: Summary of Findings of Included Studies	
Main Guideline Recommendations (*Quality of evidence/Strength of recommendation*) [a]	**Author's Conclusions**
not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment (*B/recommendation*). • For elementary school-aged children (6 to 11 years of age), the primary care clinician should prescribe FDA-approved medications for ADHD. The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended-release guanfacine, and extended-release clonidine – in that order. (*A/strong recommendation*). • For adolescents (12 to 18 years of age), the primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent (*A/strong recommendation*) • Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects (*B/strong recommendation*).	

ADHD = attention deficit hyperactivity disorder; BMI = body-mass-index; FDA = Food and Drug Administration;
[a] Guideline-specific interpretation of the designation of quality of evidence and strength of recommendation is available in Table A1

APPENDIX 5: Summary of a review of CAP-Guideline previously conducted by CADTH

In 2011, the Canadian ADHD Resource Alliance (CADDRA) published the Third edition of its Canadian ADHD Practice (CAP) guidelines. No objective or clinical question was specified for the guideline, but the authors included a list of core principles for the treatment of ADHD. The targeted users of the guideline are Canadian physicians who diagnose and treat ADHD, and the guideline applies to patients and their families living with ADHD.

Strengths of this guideline include the tools available for physicians and patients. Information, diagnostic instruments, forms, and scales that have been selected based on their validity, reliability and accessibility can be downloaded. These guidelines are considered an active document that will be revised online as new information comes available.

The major limitation was the lack of rigor used in the development of the guideline. Although consensus-based statements were identified in the text and the authors stated that evidence-based data were derived from literature cited in the reference section, the search methods and the criteria for evidence selecting were not described. Further, there was no link between recommendations and supporting evidence; and the individual recommendations were not ranked for strength based on the quality of supporting evidence.

The fact that CADDRA is an active advocacy group and the CAP guideline recommendations were not appropriately linked to evidentiary support of clearly graded quality creates uncertainty about the editorial independence of the guideline.

Summary of Pharmacotherapy Recommendations (see Table A4)

1. Long-acting stimulant drugs are recommended as first-line treatment of ADHD.
2. Short-acting and intermediate-acting stimulant drugs are recommended as second-line, with indications for use in the following situations:
    a) As-needed use for particular activities;
    b) To augment long-acting formulations early or late in the day, or early in the evening and
    c) In place of long-acting agents when the cost of the latter is prohibitive.
3. Atomoxetine and guanfacine XR are long-acting ADHD drugs recommended for use as second-line therapy

Table A4: Summary of CAP-Guideline Place in therapy Classification of ADHD Drugs					
First-Line Agents		**Second-Line Agents**			
Long-acting stimulant drugs		Short-acting and intermediate-acting stimulant drugs [a]		Long-acting non-stimulant drugs	
Brand Name	**Generic Name**	**Brand Name**	**Generic Name**	**Brand Name**	**Generic Name**
Adderall XR	Amphetamine mixed salts	Dexedrine	Dextro-amphetamine sulphate	Strattera	Atomoxetine
Biphentin	Methylphenidate hydrochloride	Dexedrine Spansule	Dextro-amphetamine sulphate	Intuniv XR [b]	Guanfacine hydrochloride extended-release
Concerta	Methylphenidate hydrochloride	Ritalin	Methylphenidate		
Vyvanse	Lisdexamfetamine dimesylate	Ritalin SR	Methylphenidate hydrochloride		

Source: CAP-Guidelines, 2011 (November 2014 version).[3] Accessed online at http://www.caddra.ca/pdfs/caddraGuidelines2011.pdf on March 10th, 2016

ADHD = attention deficit hyperactivity disorder; CAP = Canadian ADHD practice

[a] Short-acting and intermediate-acting dextro-amphetamine products can be used to augment Adderall XR or Vyvanse. Short-acting methamphetamine products can be used to augment Biphentin® or Concerta®.
[b] Intuniv XR (guanfacine extended-release) is indicated for use as monotherapy and as an adjunctive therapy to psychostimulants for the treatment of ADHD in children aged 6 to 17 years with a sub-optimal response to psychostimulant.[11]